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Short-term effects of testolactone compared to other treatment modalities on longitudinal growth and ovarian activity in a girl with McCune-Albright syndrome

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Summary

In a 6½-month-old girl with McCune-Albright syndrome, gonadotropin-independent isosexual precocity and recurrent ovarian cysts, the short-term effects of surgical therapy, cyproterone acetate (120 mg/m²/d), combined medroxyprogesterone acetate (10 mg/d), and spironolactone (50–75 mg/d) treatment, and testolactone (40 mg/kg/d) were evaluated sequentially. No significant reduction of cyst frequency was achieved with any of the medical treatments. The rate of bone maturation (ΔBA/ΔCA) was increased and the height standard deviation score (SDS) for bone age as a potential indicator of final height was decreased with surgical treatment alone and combined medroxyprogesterone acetate and spironolactone. Both parameters normalized with cyproterone acetate and testolactone. Height velocity SDS, however, was higher with testolactone (0.97 vs. 0.45).

Zusammenfassung

Ein 6½ Monate altes Mädchen mit McCune-Albright-Syndrom, isosexueller gonadotropinunabhängiger vorzeitiger Geschlechtsreife und rezidivierenden ovariellen Zysten wurde nach operativer Zystenentfernung nacheinander mit Cyproteronacetat (120 mg/m²/Tag), einer Kombination aus Medroxyprogesteronacetat (10 mg/Tag) und Spironolacton (50–75 mg/Tag) sowie mit dem Aromatasehemmer Testolacton (40 mg/kg/Tag) behandelt. Keines dieser Medikamente konnte die Rezidivneigung der ovariellen Zysten beeinflussen.

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Unter alleiniger chirurgischer Behandlung und unter Kombination von Medroxyprogesteronacetat und Spironolacton war die Geschwindigkeit der Knochenreifung (ΔBA/ΔCA) erhöht, und der Längen-Standardabweichungs-score (SDS) für das Knochenalter, ein möglicher Indikator für die Endlänge, war erniedrigt. Beide Grössen normalisierten sich unter Cyproteronacetat und Testolacton. Der Wachstumsgeschwindigkeits-SDS war jedoch grösser unter Testolacton (0,97 vs. 0,45).

Résumé

Une fille de 6 mois et demi avec un syndrome de McCune-Albright, une précocité isosexuelle indépendante des taux d'hormones gonadotropiques, avec des kystes ovariens récidivants, fut traitée successivement après le prélèvement chirurgical des kystes par de l'acétate de cyprotérone (120 mg/m²/jour), puis par une association d'acétate de medroxyprogestérone (10 mg/jour) et de spironolactone (50–75 mg/jour), et par l'inhibiteur de l'aromatase, la testolactone (40 mg/kg/jour). Aucun de ces traitements ne pouvait influencer l'apparition de récidives des kystes ovariens. Avec le traitement chirurgical simple, et le traitement d'une association d'acétate de medroxyprogestérone et de spironolactone, on trouve un accroissement de la vélocité de maturation des os et un abaissement du SDS (= nombre d'écarts type à partir de la moyenne) de la taille atteinte pour l'âge osseux comme un indicateur potentiel pour la taille adulte. Tous ces paramètres se sont normalisés par l'acétate de cyprotérone et la testolactone. La vélocité de croissance exprimée en SDS pour l'âge chronologique fut élevée par la testolactone (0,97 vs. 0,45).

Introduction

Isosexual precocity due to increased ovarian estrogen secretion with recurrent formation of ovarian cysts is the most frequent endocrine abnormality in girls with McCune-Albright syndrome (MAS) [1, 20]. The etiology of the sexual precocity is not completely established. The lack of an effect of LHRH agonists on the clinical and biochemical signs of the precocious development in young girls with MAS [5, 9] suggests that sexual precocity is maintained by gonadotropin-independent, autonomous ovarian estrogen secretion [10]. Previous attempts to treat sexual precocity with medroxyprogesterone acetate [19, 21, 22] and cyproterone acetate [26] were not successful in suppressing all signs of precocious development.

Recently, testolactone, an aromatase inhibitor specifically interfering with the final step of estrogen biosynthesis, was successfully used in the treatment of this disorder [8, 11]. It was hypothesized that testolactone acts not only by a decrease in estrogen production but also inhibits the formation and enlargement of ovarian cysts by decreasing the intraovarian estrogen concentration.

We compared the short-term effects of testolactone on longitudinal growth, rate of bone maturation, plasma steroid concentrations and the tendency to cyst formation with that of cyproterone acetate and a combined treatment with medroxyprogesterone and spironolactone, and of surgery alone in a girl with MAS.

Case report and methods

The patient, a 6½-month-old girl, had been seen by a gynecologist because of a white vaginal discharge at the age of 3 months. She was noted to develop pubic hair and breast tissue 3 weeks prior to referral to our pediatric endocrine unit. Seven days before presentation, she had her first vaginal bleeding, which continued as a spotting up to the day of her initial examination. Topical or systemic use of estrogens was excluded. The girl's length was 69 cm (50.–75. percentile for German girls), the weight was 8.9 kg (50.–90. percentile for height age). She had Tanner stage II pubic hair and breasts. Her vaginal mucosa appeared thickened and pink, there was some mucoid discharge in addition to traces of blood at the vaginal entrance. Multiple large hyperpigmented macules with irregular borders extended over the skin of her left arm, left hemithorax and left upper abdomen. Roentgenograms of the head and the trunc revealed no bone lesions. Computed tomography of the head and sonography of the adrenal glands were normal. She had a bone age of 1.3 years. Sonographic examination of the pelvic organs showed a 5.3×5.0×3.2 cm asymmetric cyst of the right ovary. Presence of a solid mass could not be excluded.

Laboratory studies confirmed an elevated plasma estradiol (E_2) concentration of 93.7 pg/ml (normal prepubertal value: <18 pg/ml). Basal serum gonadotropin levels were below detection limit of our assays (<0.5 mIU/ml; normal range during the first year: LH 0.7–2.3 mIU/ml; FSH 0.7–3.8 mIU/ml). At LHRH stimulation (25 $\mu g/m^2$) LH rose from 1.1 mIU/ml to a peak value of 2.3 mIU/ml (mean normal prepubertal rise: 4× the basal level). FSH rose from 0.5 mIU/ml to a peak value of 1.2 mIU/ml (mean normal prepubertal rise: 2.5× the basal level). hCG was undetectable (normal: <5 mIU/ml). Serum testosterone was in the normal range for pubertal girls (21.6–26.2 ng/dl; normal pubertal girls: 15–50 ng/dl).

At laparotomy, a 45 ml cyst of the right ovary and a 12 ml cyst of the left ovary were removed. A pathohistological examination showed that no malignant cells were present within the cyst wall. Hilus cell hyperplasia was seen in the ovarian stroma. The cyst fluid contained high concentrations of E_2 (>5000 pg/ml) and other steroid precursors (17-hydroxyprogesterone >5000 ng/dl, testosterone 349 ng/dl). Gonadotropins could not be detected in the cyst fluid by radioimmunoassay.

24 h after surgery plasma E2 concentrations had fallen into the normal range. 32 h after surgery the patient had an uterine bleeding.

During follow-up examinations a minor decrease of breast tissue was noted. 6 weeks later, however, a recurrence of an ovarian cyst was detected by pelvic ultrasound with a peak plasma E_2 concentration of 161 pg/ml. Laparoscopy was performed and the cyst fluid aspirated. Adhesions had formed between the ovaries and the tubes, caecum and sigma. Medical treatment was then added to the therapeutic regimen.

Treatment

The initial 3.5 months after surgery without medical treatment were used as a baseline period (Rx 0). This was followed by a 10-month period during which the patient received cyproterone acetate (Cyp A) 120 mg/m²/d in one oral dose (Rx 1). When ovarian cysts with high plasma E_2 concentrations recurred the medical treatment was changed to a combination of medroxyprogesterone acetate (MPA) 10 mg/d and spironolactone (SPL) 50–75 mg/d in 2 oral doses for a 9.5-month period (Rx 2). With the availability of testolactone for the therapy of sexual precocity in MAS [11] the treatment was then continued with testolactone 12 mg/kg/d in 4 oral doses initially and increased to a final dose of 40 mg/kg/d (Rx 3). The full therapeutic dose was given over a period of 20 months.

Protocol

The patient was seen in our outpatient clinic at least at 3-month intervals. Compliance with the medical treatment was confirmed by interview. Height velocity was calculated using at least a 6-month interval, except for the initial period without medical treatment. Each height measurement was used only once for determination of height velocity except at the start of Cyp A.

To compare height velocities at different ages, height velocity was expressed as height velocity standard deviation score (SDS). Normal height velocities for German girls and their standard deviations were taken from the tables of BRANDT [3]. By definition, 95.5% of a normal population do have a height velocity SDS between –2 and +2. Similarly, the height SDS for bone age was calculated using the tables of the Zurich longitudinal growth study [18]. Assuming that bone age and chronological age are identical in normal children, the normal range is between –2 and +2.

Blood was obtained for determination of plasma concentrations of LH, FSH, E_2 and other hormonal parameters if indicated, using direct radioimmunoassays.

Pelvic ultrasound examinations were performed with a maximum time interval between examinations of 4 months. Bone age was determined using the standards of GREULICH and PYLE [12].

Results

The patient's supine length, standing height, bone age, plasma E_2 concentrations and ovarian cyst frequency during treatment is shown in Fig. 1. Every major increment in plasma E_2 above the prepubertal level coincides with a sonographically documented cyst except in one instance, in which no pelvic ultrasound was performed. Gonadotropin concentrations were undetectable or in the lower normal range for prepubertal girls (results not shown) throughout therapy.

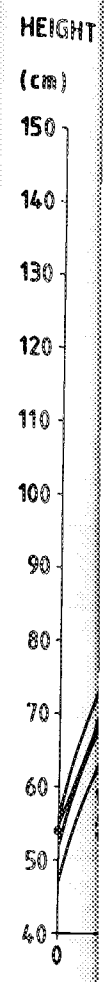
In Fig. 2 the total observation period is broken down into 4 segments with different therapy (Rx 0–Rx 3). In the first 3.5 months following surgical removal of the cysts, the patient's height velocity was greatly elevated for chronological age (3.29 cm/month, >97. percentile) with a height velocity SDS of 3.04. The rate of bone maturation was accelerated (ΔBA/ΔCA 2.64).

During Cyp A therapy (Rx 1) height velocity decreased not only in absolute terms (1.30 cm/month) but also when compared with the normal population: Height velocity SDS decreased to 0.45. The rate of bone maturation almost normalized (ΔBA/ΔCA 0.97).

During the treatment with MPA and SPL (Rx 2) absolute height velocity increased slightly; height velocity SDS increased to 1.92. This happened at the expense of an accelerated rate of bone maturation (ΔBA/ΔCA 2.77). Therapy with testolactone (Rx 3) finally led to an absolute and relative decrease in height velocity: Height velocity was 0.72 cm/moth, height velocity SDS was 0.97. A normal rate of bone maturation was achieved (ΔAB/ΔCA 1.01).

Changes in height SDS in relation to bone age as an indicator for growth potential are shown in Fig. 3. There is always a small delay between the start of a new treatment and the onset of an effect on height SDS for bone age.

No significant differences were noted between the treatment regimens with regard to plasma E_2 concentrations and frequency of ovarian cyst formation. The stage of pubertal development did not change throughout treatment.



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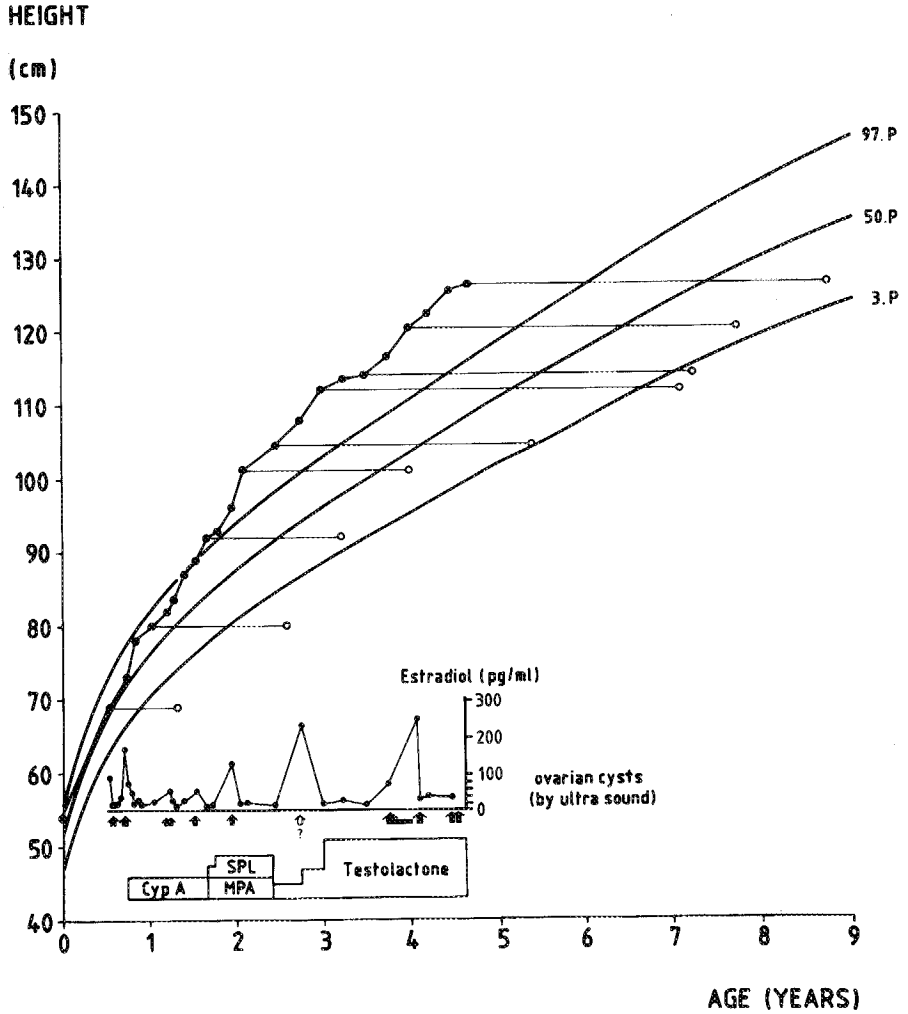


Fig. 1. Longitudinal growth, bone maturation, plasma E_2 concentrations and ovarian cyst formation in a girl with McCune-Albright syndrome under treatment (growth curve: ● = chronological age, ○ = bone age).

During treatment with testolactone, androstenedione plasma concentrations measured by a direct RIA were found to be consistently and strikingly elevated (~10^2× the upper limit of the normal range for pubertal girls) even in situations with low ovarian activity, without clinical evidence of virilization. This was due to a significant cross-reaction (37.8%) of the androstenedione antibody with circulating plasma testolactone.

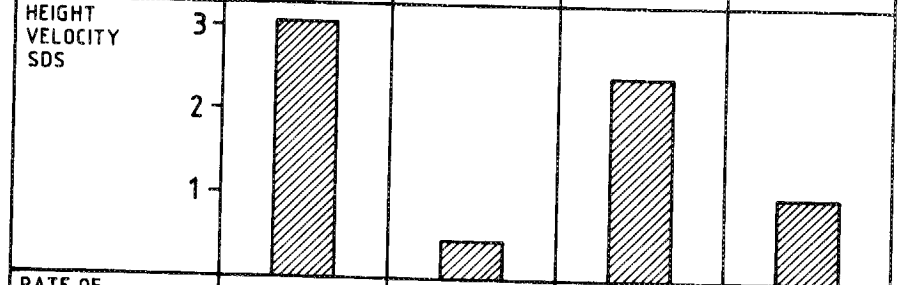
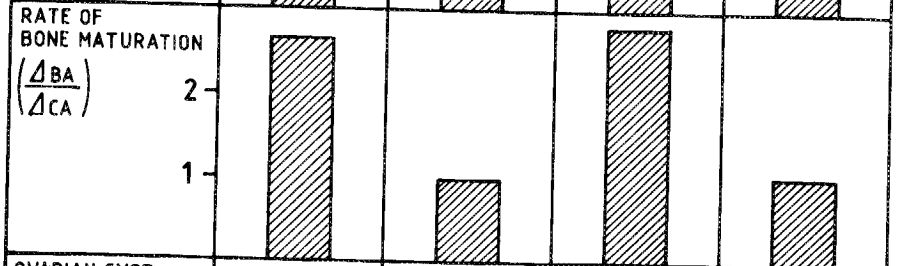
THERAPY	Rx 0	Rx 1	Rx 2	Rx 3
	SURGICAL TREATMENT (CYST EXCISION/ - PUNCTION)	Cyp A 120mg/m^2/d	MPA 10mg/d SPL 50-75mg/d	TESTOLACTONE 40mg/kg/d
DURATION OF THERAPY (MONTHS)	3,0	10,0	8,5	20,0
CHRONOLOGICAL AGE (MONTHS)	6,5-9,5	9,5-19,5	19,5-28,0	36-56
HEIGHT VELOCITY (CM/MONTHS)	3.29	1.30	1.33	0.72
HEIGHT VELOCITY SDS				
RATE OF BONE MATURATION $\left(\frac{\Delta BA}{\Delta CA}\right)$				
OVARIAN CYST FREQUENCY BY ULTRA SOUND (#)	2	3	1	4

Fig. 2. Short-term effects of 4 different therapeutical regimens on height velocity (cm/month), height velocity SDS, relative bone age advancement and frequency of ovarian cysts in a girl with McCune-Albright syndrome.

1	Rx 2	Rx 3
A /m²/d	MPA 10mg/d SPL 50-75mg/d	TESTOLACTONE 40mg/kg/d
,0	8,5	20,0
19,5	19,5-28,0	36-56
10	1.33	0.72
	1	4

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quency of ovarian cysts in a girl with McCune-

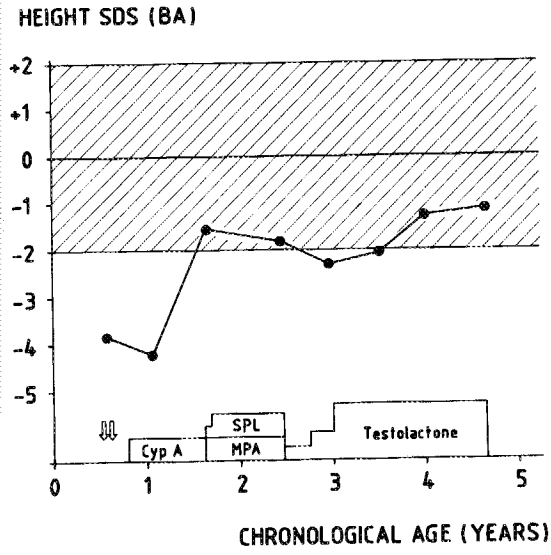

Fig. 3. Height SDS for bone age in a girl with McCune-Albright syndrome under treatment (arrows indicate cyst removal/-punction; shaded area: normal range).

Discussion

The cause of sexual precocity in MAS is not well understood. Every explanation will have to take into account the fact that the disturbance of gonadal function is only temporary and normal menstrual cycles will develop during adolescence in most girls [1]. Premature activation of the LHRH pulse generator does not play a major role in the maintenance of ovarian hyperactivity in young girls with MAS, since LHRH agonists do not have an effect on the symptoms of sexual precocity early in the course of the disease [5, 9, 10]. Most recent reports relate the multiple hormone hypersecretion to an autonomous hyperfunction of the peripheral target glands [28], but what causes autonomy remains unknown. Therefore no specific therapy exists. All therapeutic efforts are aimed at the control of breast development, pubic hair growth and menstrual bleeding, and at achieving normal adult height by prevention of premature epiphyseal fusion.

As in the majority of the reports [1, 6, 17], control of symptoms of sexual precocity by surgery in our patient was only temporary due to a recurrence of cyst formation. Therefore, and in view of normal cyclical ovarian function in later life, any surgical intervention with a high risk for ovarian adhesions, subsequent impaired genital duct patency and infertility should be avoided.

Cyp A, a 17-hydroxyprogesterone derivative with antiandrogenic, antigonadotropic, progestagenic and possibly antiestrogenic properties, has been

used to control menstrual bleeding and, less successfully, other symptoms of precocious puberty [14, 24]. No change of growth potential was observed in patients with precocious puberty treated with Cyp A [25]. Similar experience has been made in girls with MAS and a subnormal response of serum gonadotropins to exogenous LHRH [2, 15, 26]. In our patient Cyp A had no influence on the frequency of the ovarian cysts. The rate of bone maturation decreased, indicating a lesser exposition of the bone to circulating estrogens. The effect of Cyp A on bone maturation is not easily explained. Since LHRH agonists are much more effective than Cyp A in decreasing gonadotropins, an antiestrogenic effect of Cyp A rather than the antigonadotropic effect may be responsible for the observed decrease. In contrast, height velocity SDS was the lowest of the 4 treatment modalities. This may be due in part to a growth-inhibiting glucocorticoid-like activity of Cyp A observed at higher doses [13].

MPA, another 17-hydroxyprogesterone derivative used in the treatment of precocious puberty, was shown to be effective in controlling breast development, pubic hair growth, and menstrual periods in girls with MAS [19, 21, 22]. The rate of bone maturation and increased height velocity, however, were not so well controlled. Although SPL has no effect on aromatase activity in vitro [4], it interferes with the synthesis of steroid precursors in daily doses of up to 100 mg in the adult by inhibiting the cytochrome P 450 enzyme [16]. A combined treatment with MPA and SPL failed to control any symptoms of sexual precocity in our patient. A higher dose than the one used and parenteral application may be required to see an effect of MPA in MAS.

The most recent attempt to treat sexual precocity in MAS included testolactone, an aromatase inhibitor interfering with the conversion of androstenedione to estrone and testosterone to estradiol. Testolactone has been used previously to treat women with estrogen-dependent breast cancer [23], polycystic ovarian disease [7], to stimulate spermatogenesis in oligospermic men [27] and to induce regression of pubertal gynecomastia [29].

Foster et al. [11] and Feuillan et al. [8] have been following 5 girls with MAS on and off treatment with testolactone for a total treatment period of 6 to 8 months. In these girls they observed not only a sharp decline in plasma estrogen concentrations, a decrease of ovarian volumes, an increase of suppressed gonadotropin concentrations, a fall in growth rate and in the rate of bone maturation, a decreased frequency of menstrual bleeding and a minor decrease in breast size and pubic hair stage, but also an unexpected decrease in cyst formation. This led them to hypothesize that testolactone may act to reduce the estrogen concentration in or around the ovarian granulosa cell and thus inhibit the formation and enlargement of ovarian cysts.

In our patient, the cyclical pattern of elevated estrogen concentrations timely related to cyst formation did not change during testolactone although the rate of bone maturation normalized indicating lesser exposition of the bone to gonadal steroids. At the same time, height velocity SDS was higher than with

Cyp A treatment, indicating a favourable effect on prospective final height. We did not, however, observe a decrease in the frequency of cyst formation during testolactone treatment. Our findings therefore do not support a role for testolactone in reducing the inherent tendency to cyst formation of the ovary in MAS. The high androstenedione concentrations observed in our patient were not an indicator of effective aromatase inhibition but were caused to a major part by a cross-reaction of the structurally related testolactone molecule with the androstenedione antibody in the direct assay.

Although the assessment of the effects of sequential treatment in one patient is of limited value and must be used with caution, the height velocity SDS based on different measurements enables us to compare height velocities independent of chronological age.

When comparing apparent treatment effects in MAS, possible spontaneous changes in disease activity must always be taken into consideration. Frequency of cyst formation and measurable estradiol concentrations, however, did not change in our patient during the different treatments. Spontaneous long-term remissions did not occur under any of the treatment modalities. Testolactone had the best effect on the rate of bone maturation without inappropriately reducing height velocity. Height SDS for bone age as a possible indicator for adult height [25] showed continuing improvement. No side effects were noted. We conclude that the results of short-term treatment encourage the use of testolactone for the treatment of gonadotropin-independent sexual precocity in girls with MAS. Longer observation periods, however, are needed to see whether these short-term effects translate into an improved adult height prognosis.

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